REMARKS

Claims 1-32 are pending in the instant application. The claims are subject to a restriction requirement under 35 U.S.C. §121, which has been made final. Claims 1-11, 26-29, 31 and 32 are being examined on the merits with respect to the combination of is 1-(3-chlorophenyl)-4-[1-(4-cyanobenzyl)-5-imidazolylmethyl]-2-piperazinone, an inhibitor of prenyl-protein transferase and a microtubule-stabilizing agent which is paclitaxel. The claims have also been rejected for the reasons noted hereinbelow. Applicants respectfully request reconsideration of the application in light of the amendments hereinabove and the following remarks.

Consistent with 37 C.F.R. § 1.121, a version of the amended claims with markings to show changes resulting from the above amendments is presented at the end of this response.

The Examiner has implicitly made the Restriction Requirement, set forth in the Office Action of July 2, 2001, final by withdrawing the claims directed to the un-elected invention from examination. Applicants respectfully request that the Examiner expressly state that the Restriction Requirement is final. Applicants still contend that the search of the prior art for disclosure of a combination of a farnesyl-protein transferase inhibitor or prenyl-protein transferase inhibitor and an antineoplastic agent would not be an undue burden on the Examiner considering the relatively short period of time that farnesyl-protein transferase inhibitors and prenyl-protein transferase inhibitors have been known. Applicants also continue to maintain that the scope of the claimed subject matter is sufficiently narrow and definite that the results of such a search would be reasonably manageable. Applicants respectfully reserve the right to pursue the broad generic claims as originally filed in a subsequent continuation application.

However, in an attempt to address the Examiner's Restriction Requirement and to advance the prosecution of the application, Applicants have amended the claims so that the methods and compositions are directed to combinations of a prenyl-protein transferase and a microtubule-stabilizing agent. Applicants have also added new claim 34 that is directed to the instant method wherein the prenyl-protein transferase is selected from the compounds

described generically in U.S. Pat. No. 5,856,326 (cited by the Examiner). New dependent claims were also added directed to the elected species.

Applicants strongly contend that the method of treatment combining a prenyl-protein transferase and a microtubule-stabilizing agent is a reasonable claim scope based on the instant disclosure and does not place an undue burden on the Examiner in search the prior art. Applicants strongly contend that limiting the examined invention to only the elected species is not a fair compensation to the inventors for their extensive supporting experimentation. Applicants therefore respectfully urge the Examiner to examine the claims as now amended.

The Examiner has rejected Claims 1-11, 26-29, 31 and 32 under 35 U.S.C. 112, first paragraph, because the Examiner suggests that the specification does not reasonably provide enablement for the terms "therapeutic effect" in Claims 1-3, 26, 27, 31 and 32 and "cancer" or "cancerous tumors" in Claims 4-11, 28 and 29. The Examiner suggests that the terms lack clear exemplary support in the specification as filed, in light of the highly unpredictable nature of the cancer therapy art. The Examiner also suggests that there are no examples of a combination of agent effective against cancers generally.

Applicants respectfully contend that the use of the terms "cancer" and "cancerous tumors" are fully supported by the specification as filed. Applicants respectfully note that the person of ordinary (high) skill in the pharmaceutical arts would readily expect to perform extensive experimentation to determine whether a particular cancer of a patient is susceptible to the combination and what amounts and/or ratios of the individual components of a pharmaceutical combination would be clinically efficacious and that such extensive experimentation would not be undue. Applicants contend that the Examiner is imposing an arbitrarily low skill level to the person of ordinary skill in the cancer chemotherapy arts.

However, in order to advance the prosecution of the application, Applicants have amended the claims to be directed to the treatment of cancers whose growth is inhibited by administration of the prenyl-protein transferase inhibitor and the antineoplastic agent. Support for the use of this phrase may be found in the specification as originally filed on

pages 297-300. In light of this amended, which mirrors the language suggested by the Examiner on the top of page 3 of the Office Action, Applicants respectfully contend that the rejection with respect to the terms "cancer" and "cancerous tumors" under 35 U.S.C. §112, first paragraph, is now moot and should be withdrawn.

The Examiner has rejected Claims 1-7, 10, 11, 26-29, 31 and 32 under 35 U.S.C. §112, first paragraph. The Examiner suggests that the specification is enabling for the specific antineoplastic agent disclosed, but does not reasonably provide enablement for the terms "an antineoplastic agent", "a microtubule-stabilizing agent . . . . hematopoietic growth factor . . . and anthracycline family of drugs . . . podophyllatoxins". The Examiner suggests that those terms lack clear exemplary support in the specification.

Applicants note that the application as filed included figures with graphs showing the results of several *in vitro* experiments wherein a prenyl-protein transferase inhibitor was combined with a variety of conventional antineoplastic agents. Included in Figures 13-32 are the results of *in vitro* experiments combining administration of an antineoplastic selected from ara-C (an anti-metabolite), vinblastine (a vinca alkaloid), 5-FU (a anti-metabolite), colchicine (a anti-microtubule agent), doxorubicin (an anthracycline), cisplatinum (a platinum coordination complexor), epithilones A and B (microtubule-stabilizing agents), etoposide (a topisomerase inhibitor), estramustine (alkylating agent) and bicalutamide (androgen antagonist). Applicants thus respectfully contend that the application as filed discloses supporting experimentation for many of the categories of antineoplastic agents listed in Claim 6. Applicants respectfully contend that it is not a requirement that every one of the types of antineoplastic agents be analyzed in the *in vitro* assay for the specification as filed to adequately support the invention claimed in Claim 1 (or Claim 6). In light of the disclosure in the specification of additive and/or synergistic activity of a combination of a wide variety of antineoplastic agents with the prenyl-protein transferase inhibitor, Applicants respectfully contend that the Examiner's rejection of Claims 1-7, 10, 11, 26-29, 31 and 32 under 35 U.S.C. §112, first paragraph, is untenable and should be withdrawn.

The Examiner has rejected Claims 1-9, 26-29, 31 and 32 under 35 U.S.C. §112, first paragraph, because, he suggests, the specification does not reasonably provide enablement

for the phrase "prenyl-protein transferase inhibitor". The Examiner suggests that the phrase lacks clear exemplary support in the specification as filed.

Applicants respectfully contend that the application as filed does provide support for such a broad term. Applicants note that from pages 23 to 87 of the specification, an extensive list of generic structures and specific compounds is provided of examples of prenyl-protein transferase inhibitors. Applicants also note that on pages 87 to 94 of the specification a list of patent publications that describe inhibitors of prenyl-protein transferase is also disclosed. Applicants further note that on pages 112 to 267 voluminous general synthetic schemes provide guidance as to how to make such prenyl-protein transferase agents and on pages 267 to 294 detailed synthetic preparations of several specific prenyl-protein transferase inhibitors is provided. Finally, Applicants not that on pages 294 to 296 detailed descriptions of assays that can be used to test such inhibitors is provided. Applicants thus contend that the extensive description of the prenyl-protein transferase inhibitors, methods of making them and their use, in conjunction with the detailed assay description for determining *in vitro* efficacy of the combination of the prenyl-protein transferase inhibitor and antineoplastic agent fully supports that use of the phrase "prenyl-protein transferase inhibitor". Applicants therefore respectfully contend that the Examiner's rejection of Claims 1-9, 26-29, 31 and 32 under 35 U.S.C. §112, first paragraph, is untenable and should be withdrawn.

Applicants also respectfully note that new Claim 34 has been added to the application which is directed to the use, in the combination administration, of prenyl-protein transferase inhibitors related to the elected prenyl-protein transferase inhibitor.

The Examiner has rejected Claims 26, 28, 29, 31 and 32 under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the invention. The Examiner initially suggests that Claims 26, 28 and 29 are improperly drawn to the same composition. Applicants have canceled Claims 28 and 29 without prejudice. Applicants therefore respectfully contend that the rejection with respect to those claims is now moot.

The Examiner next suggests that Claims 31 and 32 are improperly drawn to the same method for forming a composition. Applicants have amended Claim 31 and have canceled Claim 32 without prejudice. In light of this amendment, which merely eliminates a duplicate claim, the rejection with respect to that duplication is now moot.

The Examiner suggests that Claims 31 and 32 are improperly drawn to the obvious method of preparing a composition by merely mixing the ingredients together. Applicants note that Claim 32 has been canceled without prejudice. Applicants next note that amended Claim 31 is directed to preparing a composition by combining the prenyl-protein transferase inhibitor and the antineoplastic agent. Applicants respectfully note that the CAFC in *Exxon v. Lubrizol* has specifically held that a claim directed to a composition having certain components does not necessarily encompass a composition formed from combining such components, if the act of combining the components changes the components (by a chemical reaction for instance). Because the act of combining a prenyl-protein transferase inhibitor and a antineoplastic agent may result in changes to those components, Applicants respectfully contend that Claim 31 is directed to a non-obvious method of preparing a specific composition, which may not necessarily be identical to Claim 26. Applicants therefore respectfully contend that the Examiner's rejection of Claim 31 is untenable and should be withdrawn.

The Examiner finally suggests that Claims 26, 28, 29, 30 and 31 are indefinite because the claims directed to the compositions fail to recite the amounts of the active agents being employed. The Examiner suggests the without a recitation of amounts, the amount of one of the agents could be so small as to be meaningless. Applicants first respectfully note that they are aware of numerous issued U.S. patents directed to novel chemical entities which have claims directed to compositions comprising such novel chemical entities and pharmaceutical carriers (but which do not specifically list the amount of the novel chemical entity in the composition). Applicants presume that compositions having "so small" amounts of that novel chemical entity would still infringe such a claim.

Applicants contend that the specification as filed clearly states that the advantage to administering a combination of the two different agents is that by affecting both prenylation

of proteins and the stability of the microtubules at the same time one could achieve a therapeutic anti-cancer effect with proportionally smaller amounts of the two components than would be required if the prenyl-protein transferase inhibitor or the microtubule stabilizing agent were administered alone. (see page 16, starting at line 26). Applicants are unclear why one of ordinary skill in the art would administer a combination of a prenyl-protein transferase inhibitor and a antineoplastic agent, but administer an amount of one that is so small as to be meaningless. Applicants respectfully contend that there would be no benefit to the patient of administering such a combination instead of only the agent administered in a meaningful amount, and that a person of ordinary skill in the art would notchoose to make such a composition.

Applicants respectfully contend that at the time of the filing of the instant application there was already extensive clinical data in the medical community detailing the appropriate amounts of the various microtubule stabilizing agents (in particular Taxol) to be administered to clinical patients as monotherapy. Applicants also respectfully contend that there was extensive knowledge in the prenyl-protein transferase inhibitor field at the time of the filing of the instant application about what assays (*in vitro* and *in vivo*) could be used to determine efficacious amounts of those compounds when administered as monotherapy (see the descriptions of the biological assays found on pages 294-300). Applicants contend that, in light of the knowledge already in the art, the amount of experimentation necessary to determine efficacious combination ratio and amounts of both the prenyl-protein transferase inhibitor and the microtubule-stabilizing agent would not be undue and it is unnecessary to specifically define those amounts in the claims. Applicants contend that the Examiner's rejection under §112, second paragraph, with respect to specific amounts of the components in the composition claims is untenable and should be withdrawn.

The Examiner has rejected Claims 1-11, 26-29, 31 and 32 under 35 U.S.C. §103(a) as being unpatentable over U.S. Patent 5,856,326 ('326 patent) taken with the Slichenmyer *et al.* reference. The Examiner notes that the class of prenyl-protein transferase inhibitors, whose use in combination with a microtubule-stabilizing agent is now being claimed, was disclosed in the '326 patent. The Examiner notes that the Slichenmyer *et al.* reference teaches that taxol was used for treating cancer in clinical trials. The Examiner states that the

two references fail to teach specific examples of the old anti-cancer agents together. The Examiner then suggests that the one of ordinary skill in the art would find ample motivation from the prior art to combine those agents, where the results obtained in so combining are "no more than the additive effects of the ingredients".

Applicants first questions what prior art would provide motivation to one of ordinary skill in the art to specifically combine the two types of therapeutic agents now claimed and examined by the Examiner. Applicants respectfully note that there is no disclosure in the Slichenmyer *et al.* reference that taxol should be advantageously combined with any other agent for the treatment of cancer. Applicants note that the '326 patent discloses that the compound disclosed therein could be co-administered with other known therapeutic agents, including cytotoxic agents (column 54, lines 33-42), but there are no specific therapeutic agents described for such a combination.

Applicants respectfully contend that at the most such a disclosure in the '326 patent would provide one of ordinary skill in the art with motivation to try the specific combination now claimed. Applicants respectfully contend that a "motivation to try" a certain combination is not sufficient for a finding of obviousness under 35 U.S.C. §103. Applicants therefore contend that the rejection under 35 U.S.C. §103 is untenable and should be withdrawn.

Applicants further note that the data provided in the figures in the instant application as filed clearly demonstrate an unexpected therapeutic effect from combining a prenyl-protein transferase inhibitor with a microtubule-stabilizing agent. Applicants note that Figures 1-3B, 6-12 and 24-27 clearly show that the combination of a prenyl-protein transferase inhibitor with a microtubule-stabilizing agent (taxol or one of the epithilone analogs) results in an activity that is greater than the mere additive effects of the ingredients. In light of the unexpected greater-than-additive effects and the lack of a clear teaching in either of the prior art references cited by the Examiner, Applicants respectfully contend that the now claimed invention is unobvious and the Examiner's rejection of Claims 1-11, 26-29, 31 and 32 under 35 U.S.C. §103(a) is untenable and should be withdrawn.

Applicants respectfully contend that the Examiner's rejections have been addressed and obviated by the above amendments and remarks, and that Claims 1-3, 9-12, 27, 30 and 31, as amended and new Claims 33-39 are allowable and an early Notice of Allowance is earnestly solicited. If a telephonic communication with Applicants' representative will aid in the advancement of the prosecution of this application, please telephone the representative indicated below.

Respectfully submitted,

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VERSION OF AMENDED CLAIMS WITH MARKINGS TO SHOW CHANGES MADE

1. (amended) A method for achieving a therapeutic effect in a mammal in need thereof which comprises administering to said mammal amounts of at least two therapeutic agents selected from a group consisting of:

a) a prenyl-protein transferase inhibitor and
b) an antineoplastic agent which is a microtubule-stabilizing agent;

wherein the therapeutic effect is the treatment of cancer whose growth is inhibited by the administration of the prenyl-protein transferase inhibitor and the antineoplastic agent.

2. (amended) The method according to Claim ~~4~~ 1 wherein an amount of a prenyl-protein transferase inhibitor and an amount of ~~an antineoplastic agent~~ a microtubule-stabilizing agent are administered simultaneously.

3. (amended) The method according to Claim ~~4~~ 1 wherein an amount of ~~an antineoplastic agent~~ a microtubule-stabilizing agent and an amount of a prenyl-protein transferase inhibitor are administered consecutively.

9. (amended) The method according to Claim ~~4~~ 1 wherein the antineoplastic agent is selected from: paclitaxel, epothilone A, epothilone B, desoxyepothilone A, desoxyepothilone B~~, doxorubicin, daunorubicin, 5-fluorouracil, etoposide, vinblastine, estramustine, cisplatin, ara-C and bicalutamide~~.

10. (amended) The method according to Claim ~~4~~ 1 wherein the prenyl-protein transferase inhibitor is selected from:

2(S)-Butyl-1-(2,3-diaminoprop-1-yl)-1-(1-naphthoyl)piperazine;

1-(3-Amino-2-(2-naphthylmethylamino)prop-1-yl)-2(S)-butyl-4-(1-naphthoyl)piperazine;

2(S)-Butyl-1-{5-[1-(2-naphthylmethyl)]-4,5-dihydroimidazol}methyl-4-(1-naphthoyl)piperazine;

1-[5-(1-Benzylimidazol)methyl]-2(S)-butyl-4-(1-naphthoyl)piperazine;

1-{5-[1-(4-nitrobenzyl)]imidazolylmethyl}-2(S)-butyl-4-(1-naphthoyl)piperazine;

1-(3-Acetamidomethylthio-2(R)-aminoprop-1-yl)-2(S)-butyl-4-(1-naphthoyl)piperazine;

2(S)-Butyl-1-[2-(1-imidazolyl)ethyl]sulfonyl-4-(1-naphthoyl)piperazine;

2(R)-Butyl-1-imidazolyl-4-methyl-4-(1-naphthoyl)piperazine;

2(S)-Butyl-4-(1-naphthoyl)-1-(3-pyridylmethyl)piperazine;

1-2(S)-butyl-(2(R)-(4-nitrobenzyl)amino-3-hydroxypropyl)-4-(1-naphthoyl)piperazine;

1-(2(R)-Amino-3-hydroxyheptadecyl)-2(S)-butyl-4-(1-naphthoyl)-piperazine;

2(S)-Benzyl-1-imidazolyl-4-methyl-4-(1-naphthoyl)piperazine;

1-(2(R)-Amino-3-(3-benzylthio)propyl)-2(S)-butyl-4-(1-naphthoyl)piperazine;

1-(2(R)-Amino-3-[3-(4-nitrobenzylthio)propyl])-2(S)-butyl-4-(1-naphthoyl)piperazine;

2(S)-Butyl-1-[(4-imidazolyl)ethyl]-4-(1-naphthoyl)piperazine;

2(S)-Butyl-1-[(4-imidazolyl)methyl]-4-(1-naphthoyl)piperazine;

2(S)-Butyl-1-[(1-naphth-2-ylmethyl)-1H-imidazol-5-yl)acetyl]-4-(1-naphthoyl)piperazine;

2(S)-Butyl-1-[(1-naphth-2-ylmethyl)-1H-imidazol-5-yl)ethyl]-4-(1-naphthoyl)piperazine;

1-(2(R)-Amino-3-hydroypropyl)-2(S)-butyl-4-(1-naphthoyl)piperazine;

1-(2(R)-Amino-4-hydroxybutyl)-2(S)-butyl-4-(1-naphthoyl)piperazine;

1-(2-Amino-3-(2-benzyloxyphenyl)propyl)-2(S)-butyl-4-(1-naphthoyl)piperazine;

1-(2-Amino-3-(2-hydroxyphenyl)propyl)-2(S)-butyl-4-(1-naphthoyl)piperazine;

1-[3-(4-imidazolyl)propyl]-2(S)-butyl-4-(1-naphthoyl)-piperazine;

2(S)-*n*-Butyl-4-(2,3-dimethylphenyl)-1-(4-imidazolylmethyl)-piperazin-5-one;

2(S)-*n*-Butyl-1-[1-(4-cyanobenzyl)imidazol-5-ylmethyl]-4-(2,3-dimethylphenyl)piperazin-5-one;

1-[1-(4-Cyanobenzyl)imidazol-5-ylmethyl]-4-(2,3-dimethylphenyl)-2(S)-(2-methoxyethyl)piperazin-5-one;

2(S)-*n*-Butyl-4-(1-naphthoyl)-1-[1-(1-naphthylmethyl)imidazol-5-ylmethyl]-piperazine;

2(S)-*n*-Butyl-4-(1-naphthoyl)-1-[1-(2-naphthylmethyl)imidazol-5-ylmethyl]-piperazine;

2(S)-*n*-Butyl-1-[1-(4-cyanobenzyl)imidazol-5-ylmethyl]-4-(1-naphthoyl)piperazine;

2(S)-*n*-Butyl-1-[1-(4-methoxybenzyl)imidazol-5-ylmethyl]-4-(1-naphthoyl)piperazine;

2(S)-*n*-Butyl-1-[1-(3-methyl-2-butenyl)imidazol-5-ylmethyl]-4-(1-naphthoyl)piperazine;

2(S)-*n*-Butyl-1-[1-(4-fluorobenzyl)imidazol-5-ylmethyl]-4-(1-naphthoyl)piperazine;

2(S)-*n*-Butyl-1-[1-(4-chlorobenzyl)imidazol-5-ylmethyl]-4-(1-naphthoyl)piperazine;

1-[1-(4-Bromobenzyl)imidazol-5-ylmethyl]-2(S)-*n*-butyl-4-(1-naphthoyl)piperazine;

2(S)-*n*-Butyl-4-(1-naphthoyl)-1-[1-(4-trifluoromethylbenzyl)imidazol-5-ylmethyl]-piperazine;

2(S)-*n*-Butyl-1-[1-(4-methylbenzyl)imidazol-5-ylmethyl]-4-(1-naphthoyl)-piperazine;

2(S)-*n*-Butyl-1-[1-(3-methylbenzyl)imidazol-5-ylmethyl]-4-(1-naphthoyl)-piperazine;

1-[1-(4-Phenylbenzyl)imidazol-5-ylmethyl]-2(S)-*n*-butyl-4-(1-naphthoyl)-piperazine;

2(S)-*n*-Butyl-4-(1-naphthoyl)-1-[1-(2-phenylethyl)imidazol-5-ylmethyl]-piperazine;

2(S)-*n*-Butyl-4-(1-naphthoyl)-1-[1-(4-trifluoromethoxy)imidazol-5-ylmethyl]piperazine;

1-{[1-(4-cyanobenzyl)-1H-imidazol-5-yl]acetyl}-2(S)-*n*-butyl-4-(1-naphthoyl)piperazine;

(S)-1-(3-Chlorophenyl)-4-[1-(4-cyanobenzyl)-5-imidazolylmethyl]-5-[2-(methanesulfonyl)ethyl]-2-piperazinone;

(S)-1-(3-Chlorophenyl)-4-[1-(4-cyanobenzyl)-5-imidazolylmethyl]-5-[2-(ethanesulfonyl)ethyl]-2-piperazinone;

(R)-1-(3-Chlorophenyl)-4-[1-(4-cyanobenzyl)-5-imidazolylmethyl]-5-[2-(ethanesulfonyl)methyl]-2-piperazinone;

(S)-1-(3-Chlorophenyl)-4-[1-(4-cyanobenzyl)-5-imidazolylmethyl]-5-[N-ethyl-2-acetamido]-2-piperazinone;

(±)-5-(2-Butynyl)-1-(3-chlorophenyl)-4-[1-(4-cyanobenzyl)-5-imidazolylmethyl]-2-piperazinone;

1-(3-Chlorophenyl)-4-[1-(4-cyanobenzyl)-5-imidazolylmethyl]-2-piperazinone;

5(S)-Butyl-4-[1-(4-cyanobenzyl-2-methyl)-5-imidazolylmethyl]-1-(2,3-dimethylphenyl)-piperazin-2-one;

4-[1-(2-(4-Cyanophenyl)-2-propyl)-5-imidazolylmethyl]-1-(3-chlorophenyl)-5(S)-(2-methylsulfonylethyl)piperazin-2-one;

5(S)-n-Butyl-4-[1-(4-cyanobenzyl)-5-imidazolylmethyl]-1-(2-methylphenyl)piperazin-2-one;

4-[1-(4-Cyanobenzyl)-5-imidazolylmethyl]-5(S)-(2-fluoroethyl)-1-(3-chlorophenyl)piperazin-2-one;

4-[3-(4-Cyanobenzyl)pyridin-4-yl]-1-(3-chlorophenyl)-5(S)-(2-methylsulfonylethyl)-piperazin-2-one;

4-[5-(4-Cyanobenzyl)-1-imidazolylethyl]-1-(3-chlorophenyl)piperazin-2-one;

2(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]-pentyloxy-3-phenylpropionyl-homoserine lactone,

2(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]pentyloxy-3-phenylpropionyl-homoserine,

2(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]pentyloxy-2-methy1-3-phenylpropionyl-homoserine lactone,

2(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]pentyloxy-2-methyl-3-phenylpropionyl-homoserine,

2(S)-[2(S)-[2(R)-Amino-3-mercapto)propylamino-3(S)-methyl]pentyloxy-4-pentenoyl-homoserine lactone,

2(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]-pentyloxy-4-pentenoyl-homoserine,

2(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]pentyloxypentanoyl-homoserine lactone,

2(S)-[2(S)-[2(R)-Amino-3-mercapto]propylaniino-3(S)-methyl]pentyloxypentanoyl-homoserine,

2(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]5- pentyloxy-4-methylpentanoyl-homoserine lactone,

2(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]pentyloxy-4-methylpentanoyl-homoserine,

2(S)-[2(S)-[2(R)-Amino-3-mercaptolpropylamino-3(S)-methyllpentyloxy-3-methylbutanoyl-homoserine lactone,

2(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]pentyloxy-3-methylbutanoyl-homoserine,

2(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]pentyloxy-3-phenylbutanoyl-homoserine lactone,

2(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]-pentyloxy-3-phenylbutanoyl-homoserine,

2(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]pentylthio-2-methyl-3-phenylpropionyl-homoserine lactone,

2(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]pentylthio-2-methyl-3-phenylpropionyl-homoserine,

2(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]pentylsulfonyl-2-methyl-3-phenylpropionyl-homoserine lactone,

2(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]-pentylsulfonyl-2-methyl-3-phenylpropionyl-homoserine,

2(S)-[2(S)-[2(R)-Amino-3-mercapto]propylaniino-3(S)-methyl]-pentyloxy-3-phenylpropionyl-methionine methyl ester,

2(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]pentyloxy-3-phenylpropionyl-methionine,

2(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]pentyloxy-3-phenylpropionyl-methionine sulfone methyl ester,

2(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]pentyloxy-3-phenylpropionyl-methionine sulfone (Compound ~~6~~ A),

2(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]-pentyloxy-3-phenylpropionyl-methionine sulfone isopropyl ester,

2-(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]-pentyloxy-3-naphth-2-yl-propionyt-methionine sulfone methyl ester,

2-(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]-pentyloxy-3-naphth-2-yl-propionyI-methionine sulfone,

2-(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]pentyloxy-3-naphth-1-yl-propionyl-methionine sulfone methyl ester,

2-(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]pentyloxy-3-naphth-1-yl-propionyl-methionine sulfone,

2-(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyllpentyloxy-3-methybutanoyl-methionine methyl ester.

2-(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]pentyloxy-3-methybutanoyl-methionine,

Disulphide of 2(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)methyl]pentyloxy-3-phenylpropionyl-homoserine lactone,

Disulphide of 2(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]pentyloxy-3-phenylpropionyI-homoserine,

Disulphide of 2(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)methyl]pentyloxy-3-methylbutanoyl-methionine methyl ester

1-(4-Biphenylmethyl)-5-(4-cyanobenzyl)imidazole

1-(4-Cyanobenzyl)-5-(4'-phenylbenzamido)ethyl-imidazole

1-(2'-Trifluoromethyl-4-biphenylmethyl)-5-(4-cyanobenzyl)imidazole

1-(4-Biphenylethyl)-5-(4-cyanobenzyl)imidazole

1-(2'-Bromo-4-biphenylmethyl)-5-(4-cyanobenzyl)imidazole

1-(2'-Methyl-4-biphenylmethyl)-5-(4-cyanobenzyl) imidazole

1-(2'-Trifluoromethoxy-4-biphenylmethyl)-5-(4-cyanobenzyl) imidazole

1-(4-(3',5'-dichloro)-biphenylmethyl)-5-(4-cyanobenzyl) imidazole

1-(2'-Methoxy-4-biphenylmethyl)-5-(4-cyanobenzyl) imidazole

1-(2'-Chloro-4-biphenylmethyl)-5-(4-cyanobenzyl) imidazole

1-(2-Chloro-4-biphenylmethyl)-5-(4-cyanobenzyl) imidazole

1-(3-Chloro-4-biphenylmethyl)-5-(4-cyanobenzyl) imidazole

1-(4-(3',5'-Bis-trifluoromethyl)-biphenylmethyl)-5-(4-cyanobenzyl) imidazole

1-(2'-Trifluoromethyl-4-biphenylmethyl)-5-(4-cyanobenzyl)-4-methylimidazole

1-(4-Biphenylmethyl)-5-(4-cyanophenyloxy)-imidazole

5-(4-Cyanophenyloxy)-1-(2'-methyl-4-biphenylmethyl)-imidazole

5-(4-Biphenyloxy)-1-(4-cyanobenzyl)-imidazole

5-(2'-Methyl-4-biphenoxy)-1-(4-cyanobenzyl)-imidazole

5-(4-(3',5'-dichloro)biphenylmethyl)-1-(4-cyanobenzyl)imidazole

1-(4-biphenylmethyl)-5-(1-(R,S)-acetoxy-1-(4-cyanophenyl)methylimidazole

1-(4-Biphenylmethyl)-5-(1-(R,S)-hydroxy-1-(4-cyanophenyl) methylimidazole

1-(4-Biphenylmethyl)-5-(1-(R,S)-amino-1-(4-cyanophenyl) methylimidazole

1-(4-biphenylmethyl)-5-(1-(R,S)-methoxy-1-(4-cyanophenyl)-methylimidazole

1-(4-Cyanobenzyl)-5-(1-hydroxy-1-(4-biphenyl)-methyl imidazole

1-(4-Cyanobenzyl)-5-(1-oxo-1-(4-biphenyl)-methyl imidazole

1-(4-Cyanobenzyl)-5-(1-hydroxy-1-(3-fluoro-4-biphenyl)-methyl)- imidazole

1-(4-Cyanobenzyl)-5-(1-hydroxy-1-(3-biphenyl)methyl-imidazole

5-(2-[1,1'-Biphenyl]vinylene)-1-(4-cyanobenzyl)imidazole

1-[N-(1-(4-cyanobenzyl)-5-imidazolylmethyl)amino]-3-methoxy-4-phenylbenzene

1-(4-Biphenylmethyl)-5-(4-bromophenyloxy)-imidazole

1-(3'-Methyl-4-biphenylmethyl)-5-(4-cyanobenzyl) imidazole

1-(4'-Methyl-4-biphenylmethyl)-5-(4-cyanobenzyl) imidazole

1-(3'-Trifluoromethyl-4-biphenylmethyl)-5-(4-cyanobenzyl) imidazole

1-(4'-Trifluoromethyl-4-biphenylmethyl)-5-(4-cyanobenzyl) imidazole

1-(3'-Chloro-4-biphenylmethyl)-5-(4-cyanobenzyl) imidazole

1-(4'-Chloro-4-biphenylmethyl)-5-(4-cyanobenzyl) imidazole

1-(2'3'-Dichloro-4-biphenylmethyl)-5-(4-cyanobenzyl) imidazole

1-(2'4'-Dichloro-4-biphenylmethyl)-5-(4-cyanobenzyl) imidazole

1-(2'5'-Dichloro-4-biphenylmethyl)-5-(4-cyanobenzyl) imidazole

1-(3'-Trifluoromethoxy-4-biphenylmethyl)-5-(4-cyanobenzyl) imidazole

1-(2'-Fluoro-4-biphenylmethyl)-5-(4-cyanobenzyl) imidazole

1-(4-(2'-Trifluoromethylphenyl)-2-Chlorophenylmethyl)-5-(4-cyanobenzyl) imidazole

1-{1-(4-(2'-trifluoromethylphenyl)phenyl)ethyl}-5-(4-cyanobenzyl) imidazole

1-(2'-Trifluoromethyl-4-biphenylpropyl)-5-(4-cyanobenzyl) imidazole

1-(2'-N-t-Butoxycarbonylamino-4-biphenylmethyl)-5-(4-cyanobenzyl) imidazole

1-(2'-Aminomethyl-4-biphenylmethyl)-5-(4-cyanobenzyl) imidazole

1-(2'-Acetylaminomethyl-4-biphenylmethyl)-5-(4-cyanobenzyl) imidazole

1-(2'-Methylsulfonylaminomethyl-4-biphenylmethyl)-5-(4-cyanobenzyl) imidazole

1-(2'-Ethylaminomethyl-4-biphenylmethyl)-5-(4-cyanobenzyl) imidazole

1-(2'-Phenylaminomethyl-4-biphenylmethyl)-5-(4-cyanobenzyl) imidazole

1-(2'-Glycinylaminomethyl-4-biphenylmethyl)-5-(4-cyanobenzyl) imidazole

1-(2'-Methyl-4-biphenylmethyl)-2-chloro-5-(4-cyanobenzyl) imidazole

1-(2'-Methyl-4-biphenylmethyl)- 4-chloro 5-(4-cyanobenzyl) imidazole

1-(3'-Chloro-2-methyl-4-biphenylmethyl)-4-(4-cyanobenzyl)imidazole

1-(3'-Chloro-2-methyl-4-biphenylmethyl)-5-(4-cyanobenzyl)imidazole

1-(3'-Trifluoromethyl-2-methyl-4-biphenylmethyl)-4-(4-cyanobenzyl) imidazole

1-(3'-Trifluoromethyl-2-methyl-4-biphenylmethyl)-5-(4-cyanobenzyl)imidazole

1-(3'-Methoxy-2-methyl-4-biphenylmethyl)-5-(4-cyanobenzyl)imidazole

1-(2'-Chloro-4'-fluoro-4-biphenylmethyl)-5-(4-cyanobenzyl)imidazole

1-(2'-Ethyl-4-biphenylmethyl)-5-(4-cyanobenzyl)imidazole

1-(2'-(2-Propyl)-4-biphenylmethyl)-5-(4-cyanobenzyl)imidazole

1-(2'-(2-Methyl-2-propyl)-4-biphenylmethyl)-5-(4-cyanobenzyl)imidazole

1-(2'-Ethyl-4-biphenylmethyl)-5-(4-(1*H*-tetrazol-5-yl))benzyl)imidazole

1-[1-(4-Cyanobenzyl)imidazol-5-ylmethoxy]-4-(2'-methylphenyl)-2-(3-N-phthalimido-1-propyl)benzene

1-(3',5'-Ditrifluoromethyl-2-methyl-4-biphenylmethyl)-5-(4-cyanobenzyl)imidazole

1-(3',5'-Chloro-2-methyl-4-biphenylmethyl)-5-(4-cyanobenzyl)imidazole

1-(3',5'-Dimethyl-2-methyl-4-biphenylmethyl)-5-(4-cyanobenzyl)imidazole

1-(3-(N-Boc-aminomethyl)-4-biphenylmethyl)-5-(4-cyanobenzyl)-imidazole

1-(3-Aminomethyl-4-biphenylmethyl)-5-(4-cyanobenzyl)imidazole

1-(4-Cyanobenzyl)-2-methyl-5-(2'-methylbiphenyl-4-yloxy)imidazole

5-(4-Cyanobenzyl)-1-(3-cyano-2'-trifluoromethylbiphenyl-4-ylmethyl)-imidazole

2-Amino-5-(biphenyl-4-ylmethyl)-1-(4-cyanobenzyl)imidazole

2-Amino-1-(biphenyl-4-ylmethyl)-5-(4-cyanobenzyl)imidazole

1-(3-Butylbiphenyl-4-ylmethyl)-5-(4-cyanobenzyl)-imidazole

1-(3-Propylbiphenyl-4-ylmethyl)-5-(4-cyanobenzyl)-imidazole

1-(4-Biphenylmethyl)-4-(4-cyanobenzyl-2-methylimidazole

1-(4-Cyanobenzyl)-5-[(3-fluoro-4-biphenyl)methyl]imidazole

1-(4-Cyanobenzyl)-5-[1-(4-biphenyl)-1-hydroxy]ethyl-2-methylimidazole

1-(4-Cyanobenzyl)-5-(4-biphenylmethyl)-2-methylimidazole

1-(4-Cyanobenzyl)-5-[1-(4-biphenyl)]ethyl-2-methyl imidazole

1-(4-Cyanobenzyl-5-[1-(4-biphenyl)]vinylidene-2-methylimidazole and

1-(4-Cyanobenzyl)-5-[2-(4-biphenyl)]vinylene-2-methylimidazole

1-(4-[Pyrid-2-yl]phenylmethyl)-5-(4-cyanobenzyl)imidazole

1-(4-[3-Methylpyrazin-2-yl]phenylmethyl)-5-(4-cyanobenzyl)imidazole

1-(4-(Pyrimidinyl-5-yl)phenylmethyl)-5-(4-cyanobenzyl)imidazole

1-(2-Phenylpyrid-5-ylmethyl)-5-(4-cyanobenzyl)imidazole

1-(2-Phenyl-N-Oxopyrid-5-ylmethyl)-5-(4-cyanobenzyl)imidazole

1-(3-Phenylpyrid-6-ylmethyl)-5-(4-cyanobenzyl)imidazole

1-(3-Phenyl-N-Oxopyrid-6-ylmethyl)-5-(4-cyanobenzyl)imidazole

1-(2-(3-Trifluoromethoxyphenyl)-pyrid-5-ylmethyl)-5-(4-cyanobenzyl)imidazole

1-(2-(2-Trifluoromethylphenyl)-pyrid-5-ylmethyl)-5-(4-cyanobenzyl)imidazole

1-(3-Phenyl-2-Chloropyrid-6-ylmethyl)-5-(4-cyanobenzyl)imidazole

1-(3-Phenyl-4-chloropyrid-6-ylmethyl)-5-(4-cyanobenzyl)imidazole

1-(2-Amino-3-phenylpyrid-6-ylmethyl)-5-(4-cyanobenzyl)imidazole

1-(2-[Pyrid-2-yl]pyrid-5-ylmethyl)-5-(4-cyanobenzyl)imidazole

N-{1-(4-Cyanobenzyl)-1H-imidazol-5-yl)methyl}-5-(pyrid-2-yl)-2-amino-pyrimidine

N,N-bis(4-Imidazolemethyl)amino-3-[(3-carboxyphenyl)oxy]benzene

N,N-bis(4-Imidazolemethyl)amino-4-[(3-carboxyphenyl)oxy]benzene

N,N-bis(4-Imidazolemethyl)amino-3-[(3-carbomethoxyphenyl)-oxy]benzene

N,N-bis(4-Imidazolemethyl)amino-4-[(3-carbomethoxyphenyl)-oxy]benzene

N-(4-Imidazolemethyl)-*N*-(4-nitrobenzyl)aminomethyl-3-[(3-carboxyphenyl)oxy]benzene

N-(4-Imidazolemethyl)-*N*-(4-nitrobenzyl)aminomethyl-3-[(3-carbomethoxyphenyl)oxy]benzene

N-(4-Imidazolemethyl)-*N*-(4-nitrobenzyl)amino-3-(phenoxy)benzene

N-(4-Imidazolemethyl)-*N*-(4-nitrobenzyl)amino-4-(phenoxy)benzene

N-(4-Imidazolemethyl)-*N*-(4-nitrobenzyl)amino-4-(phenylthio)benzene

N-Butyl-*N*-[1-(4-cyanobenzyl)-5-imidazolemethyl]amino-4-(phenoxy)benzene

N-[1-(4-Cyanobenzyl)-5-imidazolemethyl]amino-4-(phenoxy)benzene

N-(4-Imidazolemethyl)amino-3-[(3-carboxyphenyl)oxy]benzene

1-[N-(1-(4-cyanobenzyl)-5-imidazolylmethyl)-N-(4-cyanobenzyl)amino]-4-(phenoxy)benzene

(±)-4-[(4-imidazolylmethyl)amino]pentyl-1-(phenoxy)benzene

1-[(N-(1-(4-cyanobenzyl)-5-imidazolylmethyl)-N-(n-butyl)amino)methyl]-4-(phenoxy)benzene

4-[N-(1-(4-cyanobenzyl)-5-imidazolylmethyl)-N-(n-butyl)amino]-1-(phenylthio)benzene

(±)-4-[N-(1-(4-cyanobenzyl)-4-imidazolylmethyl)-N-(n-butyl)amino]-1-(phenylsulfinyl)benzene

3-[N-(4-imidazolylmethyl)-N-(n-butyl)amino]-N-(phenyl)benzenesulfonamide and

1-[N-(1-(4-cyanobenzyl)-5-imidazolylmethyl)amino]-3-methoxy-4-phenylbenzene

4-{3-[4-(-2-Oxo-2-H-pyridin-1-yl)benzyl]-3-H-imidazol-4-ylmethyl]benzonitrile

4-{3-[4-3-Methyl-2-oxo-2-H-pyridin-1-yl)benzyl]-3-H-imidazol-4-ylmethyl]benzonitrile

4-{3-[4-(-2-Oxo-piperidin-1-yl)benzyl]-3-H-imidazol-4-ylmethyl]benzonitrile

4-{3-[3-Methyl-4-(2-oxopiperidin-1-yl)-benzyl]-3-H-imidizol-4-ylmethyl}-benzonitrile

(4-{3-[4-(2-Oxo-pyrrolidin-1-yl)-benzyl]-3H-imidizol-4-ylmethyl}-benzonitrile

4-{3-[4-(3-Methyl-2-oxo-2-H-pyrazin-1-yl)-benzyl-3-H-imidizol-4-ylmethyl}-benzonitrile

4-{3-[2-Methoxy-4-(2-oxo-2-H-pyridin-1-yl)-benzyl]-3-H-imidizol-4-ylmethyl}-benzonitrile

4-{1-[4-(5-Chloro-2-oxo-2H-pyridin-1-yl)-benzyl]-1H-pyrrol-2-ylmethyl}-benzonitrile

4-[1-(2-Oxo-2H-[1,2']bipyridinyl-5'-ylmethyl)-1H-pyrrol-2-ylmethyl]-benzonitrile

4-[1-(5-Chloro-2-oxo-2H-[1,2']bipyridinyl-5'-ylmethyl)-1H-pyrrol-2-ylmethyl]-benzonitrile

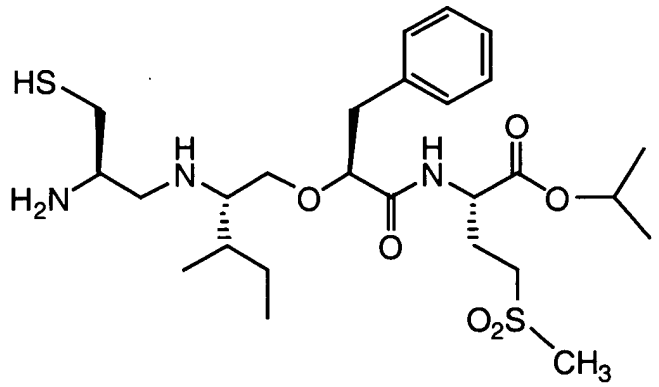
4-[3-(2-Oxo-1-phenyl-1,2-dihydropyridin-4-ylmethyl)-3H-imidazol-4-ylmethyl]benzonitrile

4-{3-[1-(3-Chloro-phenyl)-2-oxo-1,2-dihydropyridin-4-ylmethyl]-3H-imidazol-4-ylmethyl}benzonitrile

or a pharmaceutically acceptable salt, disulfide or optical isomer thereof.

11. (amended) The method according to Claim ~~4~~ 1 wherein the prenyl-protein transferase inhibitor is selected from:

2(S)-[2(S)-[2(R)-Amino-3-mercapto]-propylamino-3(S)-methyl]-pentyloxy-3-phenylpropionyl-methionine sulfone isopropyl ester (Compound A)



1-(3-Chlorophenyl)-4-[1-(4-cyanobenzyl)-5-imidazolylmethyl]-2-piperazinone;

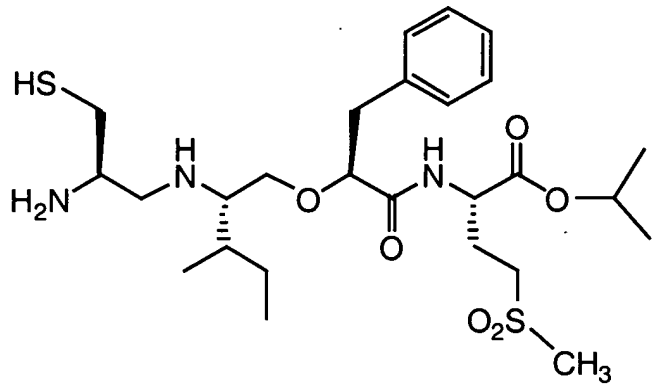
(R)-1-(3-Chlorophenyl)-4-[1-(4-cyanobenzyl)-5-imidazolylmethyl]-5-[2-(ethanesulfonyl)methyl]-2-piperazinone;

4-[1-(5-Chloro-2-oxo-2H-[1,2']bipyridinyl-5'-ylmethyl)-1H-pyrrol-2-ylmethyl]-benzonitrile and

1-[N-(1-(4-cyanobenzyl)-5-imidazolylmethyl)-N-(4-cyanobenzyl)amino]-4-(phenoxy)benzene

or a pharmaceutically acceptable salt, disulfide or optical isomer thereof.

12. (amended) The method according to Claim ~~4~~ 1 wherein the antineoplastic agent is paclitaxel and the prenyl-protein transferase inhibitor is 2(S)-[2(S)-[2(R)-Amino-3-mercapto]-propylamino-3(S)-methyl]-pentyloxy-3-phenylpropionyl-methionine sulfone isopropyl ester (Compound A)



27.(amended) ~~The pharmaceutical composition according to Claim 26~~ A pharmaceutical composition comprising an amount of a prenyl-protein transferase inhibitor and an amount of an antineoplastic agent which is a microtubule-stabilizing agent, the composition which is effective for treating cancer in a mammal in need thereof.

31. (amended) A method of preparing a pharmaceutical composition ~~for achieving a therapeutic effect in a mammal in need thereof~~

which comprisinges mixing ~~amounts of at least two therapeutic agents selected from a group consisting of:~~

~~a) a prenyl-protein transferase inhibitor and~~
~~b) an antineoplastic agent~~

an amount of a prenyl-protein transferase inhibitor and an amount of an antineoplastic agent which is a microtubule-stabilizing agent.